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| 10/568,995 | 10/12/2006 | Geoffrey Hill | 250898 | 1774 |

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| EXAMINER | |
|---|---|
| STOICA, ELLY GERALD | |

| ART UNIT | PAPER NUMBER |
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| 1647 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/568,995 | HILL ET AL. | |
| | Examiner | Art Unit | |
| | ELLY-GERALD STOICA | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12/01/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *1-51 and 62-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to amendment*

### *Status of the claims*

1. In the amendment filed on 12/01/2008 Applicant amended the independent claim 52. Claims 1-92 are pending, Claim 1-51 and 62-92 are withdrawn and claims 52-61 are currently examined.

### *Withdrawn claim rejections*

### *Claim Rejections - 35 USC § 102 and § 103*

2. The rejection of claims 52-56 and 59 under 35 U.S.C. 102(b) as being anticipated by Souza (U. S. Pat. No. 4,810,643) is withdrawn in view of the amendment to the independent claim 52.

3. The rejection of claims 52-56, 59 and 61 under 35 U.S.C. 102(b) as being anticipated by Arpinati et al. (Blood, 95, 2484-2490, 2000-cited by Applicant) is withdrawn in view of the amendment to the independent claim 52.

4. The rejection of claims 52-61 under 35 U.S.C. 102(b) as being anticipated by Molineux et al. (Experimental Hematology, 27, 1724-1734, 1999-cited by Applicant) is withdrawn in view of the amendment to the independent claim 52.

5. The rejection of claims 52-61 under 35 U.S.C. 102(b) as being anticipated by Willis et al. (Expert Opin. Biol. Ther., 2, 985-992, 2002-cited by Applicant) is withdrawn in view of the amendment to the independent claim 52.

6. The rejection of claims 52-61 under 35 U.S.C. 102(b) as being anticipated by Li EC (J. Pharmacy Soc. Wisconsin., May/June 2003, 34-39-cited by Applicant) is withdrawn in view of the amendment to the independent claim 52.

The rejection of claims 52-61 under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (Blood, 93, 4071-4078, 1999-cited by Applicant) in view of deHaan et al. (British J. Haematol., 110, 638-646, 2000--cited by Applicant) and in further view of view of Camble et al. (U.S. Pat. No. 5,320,840) is withdrawn in view of the amendment to the independent claim 52.

***New claim rejections necessitated by amendment***

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 52-57 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster PF (U.S. Patent No. 5,718,893).The claims are drawn to a pharmaceutical composition for inducing immunological tolerance when administered to a subject comprising a G-CSF derivative or biologically active fragment, homolog or variant thereof, an immune suppressing agent and a pharmaceutically-acceptable carrier. The G-CSF may be recombinant (human) and it may also comprise not-glycosylated N-methionyl human recombinant G-CSF. The G-CSF derivative may comprise an N- terminal methionyl residue. The composition may induce greater immunological tolerance when compared with administering G-CSF to humans.

Foster PF teaches that the reduction of occurrence of acute rejection of organ transplants (i.e. increased immunotolerance) is achieved by treatment with a G-CSF protein product (abstract). The term "G-CSF protein product" as used by Foster et al. is defined as naturally occurring human and heterologous species G-CSF, recombinantly produced G-CSF that is the expression product consisting of either 174 or 177 amino acids, or fragments, analogs, variants, or derivatives thereof produced either in prokaryotes (hence lacking glycosylation and an N- terminal methionyl)) or eukaryotes,

PEGylated. Foster et al. incorporated by reference the specific properties of the "G-CSF product" just mentioned (see below for specific references incorporated by Foster et al.).

In Example 1, recombinant human G-CSF (Filgrastim) was administered to high-risk, adult human liver transplant patients in addition with immunosuppressive therapy and the patients were prospectively monitored for sepsis and rejection outcomes. The immunosuppressive regimen was attained by administration of Cyclosporine and methyl prednisolone (Solu-Medrol). The G-CSF-treated patients had significantly reduced rates of infection and acute rejection when compared to patients which did not receive the G-CSF supplementation. Foster et al. dose not specifically teach a pharmaceutical composition comprising both G-CSF and an immune suppressant,

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have administered a pharmaceutical composition comprising both a G-CSF and an immunosuppressant with a reasonable expectation of success. This is because Foster used the immunosuppressant regimen in conjunction with G-CSF. Foster et al. also showed the benefits of using G-CSF in combination with immunosuppressants. Even though Foster et al. do not specifically teach a pharmaceutical composition comprising both G-CSF and an immune suppressing agent the state of the art would have allowed to obtain a single pharmaceutical combining the two compounds since they showed excellent results when treatment regimens comprising each of them where performed in combination. The motivation would be that Foster et al. also showed the benefits of using G-CSF in combination with immunosuppressants.

Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Foster PF (U.S. Patent No. 5,718,893) in view of Willis et al. (Expert Opin. Biol. Ther., 2, 985-992, 2002-cited by Applicant).

The claim adds the limitation that the G-CSF has an N-terminal methionyl residue to which a monomethoxypolyethylene glycol is covalently bound thereto.

The teachings of Foster et al where presented supra. The G-CSF with an N-terminal methionyl residue to which a monomethoxypolyethylene glycol is covalently bound thereto is not specifically taught.

Willis et al. disclose that G-CSF is used, *inter alia*, for the mobilization of peripheral blood progenitor cells for autologous and allogenic transplantation. One non-glycosylated and N-methionine bearing human recombinant G-CSF is known as Filgastrim and a PEG-Filgastrim (N-terminal mono methoxy PEGylated derivative) is used under the brand name Neulasta™, Amgen, Inc. (p. 985, abstract and section 1). The benefits of using PEGfilgastrim are disclosed as having the same or better pharmacological benefits while reducing renal clearance, cellular uptake and thus increasing the time that the protein remains effective in the circulation (p. 986, section 2). The superior results of PEG-filgastrim use with respect to the mobilization of peripheral blood progenitor cells in humans are disclosed in section 3.2.2.2.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have included immunosuppressants in the compositions used by Willis et al. with a reasonable expectation of success, since Foster used the

immunosuppressant regimen in conjunction with G-CSF. Foster et al. also showed the benefits of using G-CSF in combination with immunosuppressants.

Applicants arguments in the response filed 12/1/08 are noted, but moot in view of the amendment to claim 52 and according application of new rejections. Accordingly, no response to said arguments is required.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure refers to the prior art incorporated by Reference by Foster at al: Kuga et al., Biochem. Biophys. Res. Comm. 159: 103-111 (1989); Lu et al., Arch. Biochem. Biophys. 268: 81-92 (1989); U.S. Pat. Nos. 4,810,643, 4,904,584, 5,214,132, and 5,218,092; EP 0 335423; EP 0 272703; EP 0 459630; EP 0 256843; EP 0 243153; WO 9102874; Australian Application document Nos. AU-A10948/92 and AU-A-76380/91; WO 9012874, EP 0 401384 and EP 0 335423. See also, WO 9315211; WO 9305169; JP 04164098; WO 9206116; WO 9204455; EP 0 473268; EP 0 456200; WO 9111520; WO 9105798; WO 9006952; WO 8910932; WO 8905824; WO 9118911; and EP 0 370205.

***Conclusion***

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-18:00 M-Th and 8:30-18:00 alternative F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lorraine Spector, Ph.D.
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